Cartographie fonctionnelle cérébrale chez la souris et l’homme

Faculté de Médecine, Université de Genève
Cours à option 2ème-3ème années
« Du neurone au patient » (Prof. J.Z. Kiss, Neuroclub)
Charles.quairiaux@unige.ch

Plan
1) Historical introduction to functional brain systems, the example of language
2) Introduction to neuronal networks
3) Investigating functional brain systems and neuronal networks:
   + Example of application: Rehabilitation of prosopagnosia, presented by Nicolas Burra (Neuroclub)
4) Why using the animal model?
1. Historical introduction to functional brain systems

a. The "prehistory" of brain functions: localization of the mind...

- During early antiquity, various functions attributed to the brain (i.e. Aristotle: cooling mechanism for the blood; Platon already proposed it for the location of the immortal soul)
- Then Roman physician Galen localized mental activity in the brain based on brain injuries observations
- Descartes located the soul to the pineal gland (endocrine gland, but at least it's part of the brain)

b. The history of brain-mind relationships: globalism VS localizationism

**Globalism:**
M. Rolando (1809) and M.J.P. Flourens (1824) made lesions in the CNS of animals and studied the results:

1. Nerves, spinal cord and medulla oblongata: directly excite muscles.
2. Cerebellum: coordination of movements
3. Hemispheres: initiate the voluntary movements

"Le nerf excite; la moelle épinière lie; le cervelet coordonne; les lobes cérébraux veulent et sentent."  
However within the hemispheres they found no single region responsible for memory or cognition!

- Cognitive functions are globally distributed over the entire cortex: **globalism**

**Localizationism:**
Franz Joseph Gall (1758-1828), Johann Spurzheim (1776-1832), Paul Pierre Broca (1824-1880)

- Cognitive functions are localized to specific brain centers, cortical areas in particular
c. The example of spoken language

Paul Pierre Broca (1824-1880)
Carl Wernicke (1848-1905)

In order to communicate orally:
- Hearing sounds
- From sounds to words (sensory uncoding)
- From words to concepts (meaning)
- From meaning to words
- From words to speech movements (motor planning)
- Motor control of phonatory apparatus

Broca’s aphasia
In ~1860, Broca reported a patient, M. Leborgne (“Tan”)
Broca’s aphasia: inability to produce speech; understanding not massively impaired

Wernicke’s aphasia (~1875)
Not all language deficits are due to lesions in Broca’s area
Wernicke’s aphasia: inability to understand speech; speech production is possible but paraphasias, speech may be meaningless
Conduction aphasia = a disconnection syndrome

• Not all language deficits are due to lesions in the cerebral cortex
• Conduction aphasia: inability to repeat speech directly, understanding unimpaired, production impaired with autocorrections
• Interruption of fibre pathway: disconnection syndrome

The example of language: conclusion

Language requires the integrity of several cortical areas, anatomically and functionally linked together. Pure localisationism is not enough to explain brain functions.

This example introduces several important concepts:
• Regional specialization, functional and structural
• Serial and parallel processing
• Lateralization

d. Brodmann’s cytoarchitectonic map (~1900)

Brodmann classified cortical regions in function of their histology.

Some areal delimitations are similar to the anatomic regions lesioned in Broca’s and Wernicke’s patients

⇒ The cortex can be divided in areas of specific structures and functions.

Korbinian Broadman (1868-1918)
2. Introduction to neuronal networks

• Cortical neurons have an horizontal and vertical organization: they are organized in layers and in minicolumns.
• A minicolumn is a basic cortical network containing 100-200 neurons (excitatory and inhibitory, local and projecting)="Building block" for more specialized, more diverse cortical macrocolumns
• Minicolumns organize in macrocolumns: 50-100 minicolumns. Neurons in the same macrocolumn share functional properties e.g. in primary cortices:
  - Neurons in a macrocolumn respond to similar stimulus localizations and properties
  - Neighboring macrocolumns "represent" neighboring regions of the periphery (topological correspondence)

Thus, cortical neurons organize in networks at different scales:
- Cortical minicolumns
- Cortical macrocolumns
- Local cortical area networks
- And finally in large-scale neuronal networks

• Finally, large-scale neuronal networks are made up from several local cortical area networks interconnected by long-range projections
• Function together in all cortical functions
• The networking of discrete cortical areas into large-scale networks is dynamic (e.g. understanding written and spoken language engage partially overlapping networks)

**Functional Brain Mapping Techniques**

- TMS
- ECS
- iEEG
- EEG
- PET
- fMRI
- SPECT
- MEG

**a. Intracranial electrophysiology**

ECS and iEEG: Electrical stimulation and recordings of the cortical surface

- Both invasive, used in neurosurgical interventions where a mapping of cortical function is required (exeresis of potentially "eloquent", functionally important cortical areas).
- RQ: intracortical electrodes can also be used. However individual intracortical electrodes are used to record local activities and not large-scale networks mapping.

**b. Positron-emission tomography (PET scan; 1952)**

The earliest functional neuroimaging method

Physical principle:

- a radioactive marker administered to the subjects emits a positron
- upon encounter with an electron in biological tissue, a pair of photons is emitted and detected by the sensor array
- The amount of radioactivity in a given brain region reflects metabolism (hemodynamic response) and indirectly neuronal activity
- Inconvenients: radioactive, low temporal resolution
- Advantage: non-invasive

→ 2D or 3D structural imaging

Physical principle: The spin of protons (especially hydrogen nuclei in water molecules) is aligned along a magnetic field. The alignment of the proton spin is briefly perturbed by a radiofrequency pulse. MRI measures parameters reflecting the realignment of proton spin along the main magnetic field: T1 (longitudinal relaxation), T2 (transversal relaxation).

The main magnetic field lines down the magnet's centre.

The spin of the protons lines up with B0, generating a net magnetization M0, aligned with B0, along what is by convention, the x-axis. M0 is then manipulated to give an MRI image.

\[ T1: \]
- Sang, graisse: blanc
- WM: gris clair++
- GM: gris foncé+
- CSF : hyposignal noir

\[ T2: \]
- CSF: hypersignal blanc
- Graisse, WM, GM: gris
- Sang: hyposignal noir

IRMf: Functional magnetic resonance imaging (1992)

Neuronal activity induces an increase in O2 consumption and, in response, a disproportionate increase in regional cerebral blood flow and oxy-hemoglobin.

- This increase in oxy-Hb in turn decreases the local concentration in deoxy-hb.
- fMRI measures the reduction in deoxy-Hb (which is paramagnetic, as compared to oxy-Hb, diamagnetic) that increase MRI signal!
- fMRI signal reflects the Blood Oxygenation Level-Dependant (BOLD) signal

The HRF is slow, peaking at 5 sec after the change in MR. Therefore inconvenient: low temporal resolution. However, better spatial and temporal resolution than PET (1 vs 250 mm3; 1.5 vs 100 sec) and no tracers injections!
d. Transcranial magnetic stimulation (TMS)

Technique médicale utilisée dans le diagnostic des maladies neurologiques, comme outil d’investigation scientifique en neurosciences et comme traitement clinique dans certaines affections psychiatriques. Elle consiste à appliquer une impulsion magnétique sur le cerveau à travers le crâne en plaçant une bobine à la surface de la tête, ce qui induit un champ électrique modifiant l’activité des neurones situés dans le champ magnétique de la TMS.

Applications:
• Clinique: traitement dans la dépression et des hallucinations auditives; enregistrement des potentiels évoqués moteurs (PEM), c’est-à-dire de l’activité électrique musculaire survenant après que de potentiels d’action générés dans le cortex cérébral moteur par une impulsion magnétique se soient propagés jusqu’au muscle à travers les voies nerveuses motrices centrales et périphériques. Ceci renseigne notamment sur l’état fonctionnel de la voie cortico-spinale.
• En recherche: la TMS est considérée engendrer une lésion artificielle (et temporaire) de la zone visée par le champ magnétique. En observant les modifications que cela entraîne dans les performances cognitives, on peut en déduire des informations sur le rôle fonctionnel de la région soumise au champ magnétique.

![Diagram of TMS](image1)

e. Electroencephalography (EEG, 1929) and magnetoencephalography (MEG)

Principe: L’EEG est l’enregistrement de l’activité électrique cérébrale au moyen d’électrodes placées sur le scalp.

- Synchronous activity in neurons generates an electric and a magnetic field that can be detected using electrodes (EEG) or coils (MEG)
- In contrast to PET or fMRI, EEG and MEG measure direct correlates of neuronal activity
- Advantages: high temporal resolution allows studying synchronization between areas (useful in a large-scale network perspective!)
- Inconvenients: low spatial resolution

![Diagram of EEG and MEG](image2)
Some applications:

In clinical environment, spontaneous EEG are useful for diagnosing epilepsy or tumors, predicting epileptic seizures, detecting abnormal brain states (coma, brain death,...) or classifying sleep stages.

Event-related potentials (ERPs) are used to investigate more specific perceptual or cognitive processes (need numerous stimulus repetitions and more data processing ). The ERPs or EPs are characterized by a series of deflections (or components) classically labeled according to their polarity (positive/negative) at specific recording sites and typical latency (N74, P300,...). Used in all areas of neuroscience to investigate the spatiotemporal pattern of brain activity in sensory, motor and cognitive processes. Also used by clinicians to check the connection.

Electrical neuroimaging (mapping and source localization): for example in pre-chirurgical investigations in order to remove epileptic foyer, or to preserve important functional regions before tumor dissection. Latest development include the combination of EEG and fMRI to increase spatial resolution of EEG.

Evoked potentials (EP) or Event Related Potentials (ERP)

Prérequis: Les électrodes enregistrent PE de très faible amplitude (0.1-20 microvolts), au milieu de signaux biologiques de plus forte amplitude (EMG, ECG…) et de bruits électriques.

➔ Amplification, Filtration et Moyennage!!

Les données sont moyennées à travers les répétitions de la condition expérimentale par rapport au Trigger de stimulation.
Les moyenne résultantes sont des courbes de différences de potentiel en fonction du temps.
Au niveau occipital (cortex visuel) les réponses se présentent sous forme d’une succession d’oscillations qui comportent des pics positifs et négatifs: P1 (P50), N1 (N70), P2 (P100), N2, etc.

On mesure:

- La latence (ms) d’un pic, la différence des latences entre pics (par exemple: P1-N1), la différence des latences entre chaque œil.
- L’amplitude (μV) maximale de chaque pic. Aussi: différence des amplitudes entre chaque œil.

Des modifications de latences et/ou d’amplitudes des pics nous renseignent sur la présence éventuelles de lésions périphériques ou centrales sur la voie sensorielle.

**Exemple: Potentiel Evequé Visuel (PEV)**

**EEG**

1. **EEG de Haute Résolution**: 64 jusqu’au 256 électrode


The location of active neuronal populations (sources) can be traced from EEG/MEG recordings at the head surface if a large number of electrodes is used.

the inverse problem: the estimation of the sources given the measured signals, is "under-determined" ... several sources can explain a given configuration of epicranial potentials.

Advantages: increases spatial resolution

Inconvenients: still lower spatial resolution than fMRI

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High resolution EEG recordings

Recording of the structural MRI

Recording of the 3D electrode positions

Segmentation of the brain surface

Mapping of the scalp electric field

Definition of the grey matter

Inverse solution calculation

Definition of the solution space within the gray matter
Ex: Résultats PEV chez les sujets normaux

OEil Gauche

OEil Droit

N = 40

EX: Cas Cliniques: Scléroses en Plaques

OEil Gauche

OEil Droit

Normaux

I.H. (f, 25 ans): symptômes visuelles bilat. RRM6

P100: 112 ms

P100: 111 ms

C.A.G. (f, 27 ans): symptômes visuelles à G CIS

P100: 135 ms

P100: 124 ms

H. F. (M, 45 years): symptômes visuelles bilat. SPMS

P100: 177 ms

P100: 141 ms
Ex: Electric Neuroimaging in Epilepsy

Averaged Spike (128 channel recording)

Localisation de foyers épileptiques

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Exploring large-scale neuronal networks in the mouse and rat

Why do brain research in rodents?!
- Not much is known about the neurophysiological and molecular basis for network function
- Needed: invasive electrophysiology and morphology, experimental lesions, environmental manipulations, pharmacological studies, and genetic manipulations
- Impossible to do in humans, ethically controversial and too expensive in monkeys (and cats)

Humans and rodents brains share fundamental physiological, histological and anatomical characteristics

- Fundamental units: neurons and astrocytes
  - Human brains: 100 billion neurons
  - Human cortex: 12 billion
  - Rat cortex: 15-30 million
  - Mouse cortex: 4 million
- Neurons make about 10,000 synapses each ($10^{15}$ synapses...)

The rodent model for neuronal networks

- Somatotopic maps

The mouse/rat whisker-to-barrel cortex system: an ideal model to study experience and lesion dependant plasticity, development and maturation of neuronal networks, physiological bases of sensory processing.
Additional notes on the physiological basis of the EEG

The EEG measures the potential difference between two electrodes. Each pair of electrodes measures a different waveform across time. The EEG measures some local electrical activity changes.

- EEG measures electrical activity that varies in the millisecond range.
- Grande distance entre l'électrode et les neurones ↠ l'activité synaptique de peu de neurones n'est pas visible sur le scalp.

Purves: Neuroscience

Synchronisation of the activity of neuronal populations

Weak Synchronisation → irregular signal with small amplitude
Strong Synchronisation → regular signal with large amplitude
Additional notes on the physiological basis of the EEG

Orientation of the synchronously active neuronal population

Radial orientation → Closed field

Parallel Orientation → Open (dipolar) field

Columnar organization of pyramidal neurons

EEG oscillations

The oscillations measured with the EEG are due to reciprocal interactions of excitatory and inhibitory neurons in intrinsic neuronal circuit loops.
Summary

- EEG records *postsynaptic potentials* and not action potentials.

- EEG records the activity of *pyramidal neurons* because of their parallel orientation.

- EEG records the *synchronous activity* of large number of parallel organized neurons that together generate a sufficiently strong dipolar field.